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EXAMINER	
HUMPHREY, DAVID HAROLD	
ART UNIT	**PAPER NUMBER**
1643	

DATE MAILED: 03/27/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/687,396	FRACKELTON ET AL.	
	Examiner	Art Unit	
	David Humphrey	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 February 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-18* is/are pending in the application.

4a) Of the above claim(s) *3-6,8,9 and 12-18* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,7,10 and 11* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *15 October 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *02/28/06;08/13/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restriction

1. The Office acknowledges the receipt of Applicants' election and Amendment, filed on 02/28/06. Applicants elect Group II, claims 2, 10, and 11, with traverse. Applicants further elect the species breast cancer

The traversal is on the grounds that although the claims of Group I and II are patentably distinct, a search and examination of the claims of Groups I and II can be made without serous burden and thus should be examined in one application. Applicants argue that administration of an agent that inhibits expression of p46 Shc and/or p52 Shc would have extensive overlap with a search for a method that involves inhibiting the activity of p46 Shc and/or p52 Shc. Applicants further argue that the same reasoning applies to Groups IV and V, and Groups X and XI. Applicants' arguments are found persuasive. Groups I, II, IV, and V (claims 1, 2, 4, 5, 7, and 10-12) of the previous restriction requirement are now combined into Group I and will be examined together. Groups III and VI (claims 3, 6, 8, 9, and 10-12) are now combined into Group II but will not be examined in this application

2. Claims 1-18 are pending.

Claims 3, 6, 8, 9, and 13-18 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim.

Claims 1, 2, 4, 5, 7, 10-12, are under examination.

Claim objections

3. Claims 10-12, are objected to because of the following informalities: they are partially dependent on non-elected subject matter. For example, claims 10 and 11 depend on claims 1, 2, or 3, and claim 12 depends on claims 4, 5, or 6. Of the above-mentioned claims, claims 3 and 6 are drawn to non-elected subject matter. Appropriate correction is required.

Claim Rejections - 35 USC § 112, second paragraph

4. The following is a quotation of the second paragraph of 35 U.S.C. §112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 2, 5, and 10-12, are rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 2 and 5 are vague and indefinite for the recitation of "an agent that inhibits the **activity** of p46 Shc and/or p52 Shc". Since Shc is an adaptor protein that does not catalyze a reaction, it is unclear what activity Shc possesses. One possible interpretation is that the agent prevents Shc binding to a Shc binding partner. Alternatively, the agent could prevent the formation of a Shc-containing signaling complex which in turn activates or inactivates other downstream effector proteins.

Clarification and/or correction are required.

Claim Rejections - 35 USC § 112, first paragraph

5. The following is a quotation of the first paragraph of 35 U.S.C. §112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 1, 2, 4, 5, 7, and 10-12, are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The Written Description Guidelines for examination of patent applications indicates, "the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical characteristics and/or other chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show applicant was in possession of the claimed genus. " (See MPEP 2164).

The specification does not reasonably provide a written description for a method for treating a subject afflicted with a proliferative disorder comprising administering any

agent that inhibits the activity or expression of p46 and/or p52 Shc. In addition, the specification does not reasonably provide a written description for a method of inhibiting a cell by administering any agent that inhibits the activity or expression of p46 and/or p52 Shc. Thus, the full scope of the claims is a method that utilizes any agent. "Agent" encompasses a huge number of possible compounds which include any organic or inorganic chemical, see Specification, page 13, lines 12 and 13. According to the specification, examples of agents include amino acid, amino acid oligomer, amino acid polymer, natural or synthetic polypeptide or synthetic analog thereof, including phosphomimetic derivatives, any protein, antibodies, antibody fragments, any enzymatic derivative or analog thereof, and any phospholipids, just to name a few, see Specification, page 13, line 13 through page 14, line 20.

The specification has not identified any key structural or functional requirements for an agent that would inhibit p46 and/or p52 Shc. Also, the specification does not disclose how an agent that inhibits p46 and/or p52 Shc would not also inhibit p66 Shc. Kisielow M. et al. (Biochem. J. 363: 1-5, 2002) teach that ShcA isoforms, p66, p52 and p46, differ only in their N-terminal regions and are derived from two different transcripts, namely p66 and p52/p46 Shc. Kisielow et al. further teach that an siRNA sequence derived from p52/p46 Shc suppressed both p66 and p52/p46 Shc, see page 1, Abstract, bridging sentence between left and right columns.

To provide adequate written description and evidence of possession of a claimed genus, any agent that when administered to a subject inhibits p46 and/or p52 Shc, the specification must provide sufficient distinguishing identifying characteristics of the

genus. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, and structure/function correlation. In this case, the only agent disclosed is a dominant negative form of Shc, see Specification, pages 29 and 30. Other than the dominant negative Shc construct, no other compounds or chemicals or proteins are provided that would indicate that Applicants are in possession of the genus of any agent, organic or inorganic, that inhibits p46 and/or p52 Shc. Accordingly, in the absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide adequate written description of the claimed genus and one of ordinary skill in the art would conclude that Applicant was not in possession of the broadly claimed genus.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116). As discussed above, the skilled artisan cannot envision the compounds of the encompassed genus of agents, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. See Fiers v. Revel, 25 USPQ2d 1601 at 1606 (CAFC 1993) and Amgen Inc. v. Chugai

Pharmaceutical Co. Ltd., 18 USPQ2d 1016.

One cannot describe what one has not conceived. See Fiddes v. Baird, 30 USPQ2d 1481 at 1483. In Fiddes v. Baird, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

See University of Calfornia v. Eli Lilly and Co. 43 USPQZd 1398. Applicant is directed to the Revised Interim Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, paragraph 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

Applicant is reminded that Vas-Cath makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

7. Claims 1, 2, 4, 5, 7, and 10-12, are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of inhibiting p46 Shc and/or p52 Shc in a cell comprising administering a dominant negative Shc DNA construct to a cell, does not reasonably provide enablement for a method of inhibiting p46 Shc and/or p52 Shc in a cell or patient by administering any agent. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The factors to be considered in determining whether undue experimentation is required are summarized In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir,1988). The court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue' not 'experimentation'. " (Wands, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the breadth of the claims, (2) the nature of the invention, (3) the state of the prior art, (4) the level of one of ordinary skill, (5) the level of predictability in the art, (6) the amount of direction provided by the inventor, (7) the existence of working examples, (8) the quantity of experimentation needed to make or use the invention based on the content of the disclosure.

Nature of the invention and breadth of the claims: The claims are drawn to a method for treating a subject afflicted with a proliferative disorder comprising administering to the subject a therapeutically effective amount of an agent that inhibits the expression or the activity of p46 Shc and/or p52 Shc in the subject. The claims are also drawn to a method of inhibiting the expression or activity of p46 and/or p52 Shc in a cell. Claim 7 recites the method wherein the agent is selected from siRNA, a ribozyme, or a DNAzyme. Claim 10 recites the method wherein the subject is human. Claim 11 recites the method wherein the proliferative disease is prostate cancer, ovarian cancer, or breast cancer. Claim 12 recites the method wherein the cell is a prostate cancer cell, an ovarian cancer cell or a breast cancer cell. Depending on the

agent administered, the claims could encompass many different types of treatment such as on gene therapy, protein therapy, immunotherapy with antibodies, and chemotherapy, for example. The term "agent" encompasses peptides, proteins, mutated proteins or peptides, antibodies, antibody fragments, plant extracts, naked DNA, single and double-stranded RNA, entire classes of organic compounds, chemical derivatives, inorganic compounds, etc. Therefore, the scope of the claims is very broad.

The amount of direction provided by the inventor and the existence of working examples: The specification provides no guidance on the inhibition of p46 and/or p52 Shc as a method of therapy or treatment. In the specification, there is a section titled "Therapeutics" (see pages 40 and 41). However, this section provides only a brief contemplation of treatment of patients having breast cancer or prostate cancer by using an agent that alter the cellular amounts of any Shc isoforms. There is no indication of what types of agents should be used and how these agents should be administered to selectively target cancer cells in patients. There are no working examples that demonstrate the administration of any agent that inhibits p52 and/or p46 Shc to any subject afflicted with a proliferative disorder. The only agent described in the specification was a dominant negative p52 Shc protein that when transfected into to a prostate cancer cell line inhibited cell proliferation, see Specification, page 29, lines 25-29. Tumor cells containing the dominant negative Shc implanted into mice did not grow in comparison to prostate cancer cells expressing wild-type Shc that did grow, see Specification, page 29, lines 29-35. However, these examples are not methods of treatment. The implanted mice do not have proliferative disorders. There is no

demonstration or examples of administering an agent to a subject afflicted with a proliferative disorder, which in any way reduces the growth of a pre-existing tumor or provides any therapeutic benefit.

The specification does provide guidance on the prognostic or predictive value of determining the ratio of p52 and p46 Shc to p66 Shc, see figure 7. A higher ratio of p52 and p46 to p66 Shc is correlated with disease recurrence in prostatic cancer tissue biopsies, see figure 7. However, correlation of the increased levels of p46 and p52 Shc to recurrent cancer does not necessarily mean decreasing the level of p46 and p52 Shc would be therapeutic. Correlation does not imply causation. Just because two variables are highly correlated does not mean that one causes the other. To establish that the administration of agents that inhibit p46 and/or p52 Shc are therapeutic, designed experiments must be performed. There are no such experiments in the instant specification. In addition, the specification has not disclosed any agents that could be used to selectively inhibit the binding of p46 and/or p52 Shc but not the p66 isoform of Shc. Protocols used to administer the agents to the subjects have also not been disclosed. Even if causality is determined, targeting specific proteins, not to mention specific isoforms of the same protein, within tumors is unpredictable as evidenced by the prior art.

The state of the prior art and the level of predictability in the art: The prior art regarding the targeting of a specific protein for cancer therapy is unpredictable. For example, Blum et al. (Drug Resistance Updates 8:369-380, 2005) teach that although constitutive activation of Ras pathways plays a critical role in cancer development and

maintenance, inhibitors of such pathways already in use for cancer therapy have shown only partial success in the most deadly types of human cancers, see page 369, Abstract, lines 1 and 2. Blum et al. further teach that even combinations of Ras-pathway inhibitors with classic cytotoxic drugs or irradiation are insufficient, see Abstract, lines 2 and 3. Therefore despite the strong evidence for the key role of active Ras and its effector pathways in human oncogenesis, efforts to target Ras or its upstream regulators and downstream effectors for cancer therapy have so far met with only partial success, see page 370, right column, section 3, lines 1-4. Blum et al. further teach that one possible reason for only partial success is targeting a single oncogene in the presence of additional tumorigeneic lesion might not be sufficiently effective against cancer, see page 371, left column, first complete paragraph, lines 1-4. Blum et al. teach another possible reason for the limited success of Ras inhibitors in cancer therapy is that many of the pathways downstream of Ras are controlled not by other proteins in addition to Ras, see page 371, second full paragraph, lines 1-3. For example, the PI-3-Kinase pathway is activated by both Ras-dependent and Ras-independent mechanisms, see page 371, right column, lines 1-3. Therefore inhibition of Ras would not be sufficient to block that pathway. While Ras is clearly not the same protein as Shc, the comparison is fitting since both proteins exist in several isoforms and the isoforms of Shc, like Ras, have a high degree of sequence homology and interact with other proteins upon phosporylation.

Ravichandran KS (Oncogene 20: 6322-6330, 2001; cited in Applicants' IDS) teaches that although initially identified as an SH2 containing proto-oncogene involved

in growth factor signaling, Shc has been implicated in signaling via many different types of receptors, such as growth factor receptors, G-protein coupled receptors, hormone receptors and integrins, see page 6322, Abstract, lines 1-8. Ravichandran teaches that as of May 2001, there are over 1300 citations on Shc describing its involvement in signaling via many different receptors but that a number of issues related to Shc function remain unanswered, see page 6327, right column, "Where do we go from here?" section, lines 1-4. Ravichandran teaches that the p52 Shc-mediated MAPK activation is well established but that this is unlikely to be the sole reason for the use of Shc by many receptors, since most receptors use more than one mechanism to activate the Ras/MAPK pathway, see page 6228, left column, lines 3-6. Ravichandran further teaches that dominant negative Shc or loss of Shc expression often only results in a partial loss of MAPK activation, see page 6228, left column, lines 6-8. Therefore, addressing the role of Shc under in vivo conditions in different tissues would require generation of conditional knockout mice, which can then be induced to lose Shc expression in a tissue specific and temporal manner. Another issue that is not addressed in the specification is how to selectively target diseased cells but not healthy cells in the subject since Shc A isoforms are ubiquitously expressed, see Ravichandran, page 6322, Abstract, lines 8-11. Ravichandran concludes that a combination of genetic, structural, and biochemical studies may be need to better understand and define the downstream effectors of Shc other than MAPK pathway, see page 6328, right column, last paragraph.

Moreover treatment of proliferative conditions, such as cancer, in general is unpredictable. For example, Jain (Scientific American July 1994) discloses barriers to the delivery of drugs into solid tumors. These impediments include (1) Non-uniform blood delivery to all areas of the tumor in which some areas of the tumor receive therapeutic agents and other areas of the tumor receive no therapeutic agent at all. (Page 60 col. 3); (2) Increased viscosity of blood in the tumor itself which also hinders drug delivery to the tumor (see paragraph bridging pages 60 and 61); (3) High liquid pressures in the interstitial matrix can retard the delivery of large therapeutic agents, such as antibodies, into tumors (page 61, Col. 1, paragraph 1); (4) Convection is a necessary mechanism by which larger therapeutic molecules such as antibodies, reach target cells which are not directly fed by the vasculature. Convection is not observed in large tumors (defined as more than ½ centimeter in diameter, page 62, col. 1) and convection is necessary for adequate drug delivery of molecules having a molecular weight of more than 5000 (page 61, col. 1 through page 63, col. 3) and (4) Molecules as large as antibodies (i.e., MW=150,000) would require several months to reach a uniform concentration in a tumor that measures 1 centimeter in radius (page 63, col. 2). Moreover, treatment of cancer in a host is quite unpredictable. Additionally, it was revealed that the drug Endostatin is unlikely to be the kind of across-the-board cancer cure that many had hoped for. Out of the 61 terminally ill patients tested, not one recovery had been seen (MSNBC News Services, "Mixed results on new cancer drug", November 9, 2000). Hence, it would not be predictable that a compound drawn to

inhibiting cell proliferation would be effective in a host in need thereof- such as a host suffering from cancer.

Gura (Science 278: 1041-1042, 1997) also discusses the shortcomings of potential anti-cancer agents including extrapolating from in vitro to in vivo protocols, the problems of drug testing in knockout mice, and problems associated with clonogenic assays. Indeed, since formal screening began in 1955, thousands of drugs have shown activity in either cell or animal models, but only 39 that are used exclusively for chemotherapy, as opposed to supportive care have won approval from the FDA (page 1041, 1st column) wherein the fundamental problem in drug discovery for cancer is that the model systems are not predictive.

A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed inventions without undue experimentation. In re Wright, 27 USPQ2d 1510 (CAFC). The disclosure does not demonstrate sufficient evidence to support the applicants' claim to a method for treating a subject afflicted with a proliferative disorder by administering to a subject an agent which inhibits the activity or expression of p46 and/or p52 in the subject. All of the factors considered in the sections above, underscores the criticality of providing working examples in the specification.

Quantity of experimentation needed to make or use the invention based on the content of the disclosure: In view of the Wands factors considered above, one of ordinary skill in the art would conclude that a method for treating a subject afflicted with

a proliferative disorder by administering to a subject an agent which inhibits the activity or expression of p46 and/or p52 in the subject, would require undue experimentation in order to use the invention as claimed by the Applicants.

8. NOTE: For examination and application of the prior art in view of the enablement rejection above, the claims will be interpreted to methods of inhibiting p52 and/or p46 Shc in a prostate cancer or breast cancer cell by administering an agent.

Claim Rejections - 35 USC § 102

9. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

10. Claims 1, 2, 4, 5, 7, and 10-12, are rejected under 35 U.S.C. 102(b) as being anticipated by Nolan MK et al. (Int. J. Cancer 72: 828-834, 1997; cited in Applicants' IDS) as evidenced by Kisielow M et al. (Biochem. J. 363: 1-5, April 1, 2002).

The claims are drawn to a method of inhibiting p46 and/or p52 Shc in breast cancer cells by administering an agent that inhibits p46 and/or p52 Shc protein activity or expression.

Nolan MK et al. teach a method of inhibiting Shc expression using RNAi in the breast cell line, MCF-7, see Abstract, lines 7 and 8, 11-13, and 17-20. While Nolan

does not explicitly teach the inhibition of p52 and p46 Shc, inhibition of a sequence shared by the two different transcripts of Shc, p66 and p52/p46 Shc, inhibits all isoforms as evidenced by Kisielow et al, see Kisielow, page 1, Abstract, right column, lines 1 and 2.

11. Claims 1, 2, 4, 5, 7, and 10-12, are rejected under 35 U.S.C. 102(b) as being anticipated by Stevenson LE et al. (Cell Growth and Differentiation 10: 61-71, 1999; cited in Applicants' IDS).

The claims are drawn to a method of inhibiting p46 and/or p52 Shc in breast cancer cells by administering an agent that inhibits p46 and/or p52 Shc protein activity or expression.

Stevenson et al. teach a method of inhibiting Shc by transfecting several breast cancer cell lines with a dominant negative Shc construct which interferes with Shc signaling to Ras, see page 61, Abstract, lines 6-8. The dominant negative Shc fusion product expressed all three ShcA isoforms, p66 Shc, p52 Shc, and p46 Shc, see page 63, figure 2.

Conclusion

12. No claim is allowed.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Humphrey whose telephone number is (571) 272-5544. The examiner can normally be reached on Mon-Fri 8:30AM-5PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on (571) 272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

David Humphrey, Ph.D.

March 17, 2006

LARRY R. HELMS, PH.D.
SUPERVISORY PATENT EXAMINER